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13. ABSTRACT (Maximum 200 words)  We have investigated the use of capillary electrophoresis (CE) for the modeling of octanol-water partition coefficients. Reversed-phase liquid chromatography (RPLC) is likely the most used method for estimation of octanol-water partition coefficients, with correlations from approximately 0.5 to 0.000, depending on the column and compounds tested. RPLC will never be a reliable method, however, because of variability in the chemistry of the stationary phase from column to column. Capillary electrophoresis is a much simpler system, as there is no true stationary phase, and there should be dramatically less variation from laboratory to laboratory. We have shown that CE can give a single point estimate of the octanol-water partition coefficient. Specifically, micellar electrokinetic capillary chromatography (MEKC), the micellar variant of the CE experiment, was evaluated as an a priori predictor of n-octanol-water partition coefficients ( $\log K_{o/w}$ ). Over 100 solutes with widely varying functionality were used to construct a universal calibration for estimation of octanol-water partition coefficients with $r^2 = 0.825$ . The calibration covers in excess of 9 orders of magnitude in $\log K_{o/w}$ . This method reduces the laboratory-to-laboratory variability and the long analysis time due to the multiple mobile phases necessary in current HPLC methods while retaining many of the desired advantages of chromatographic techniques.				
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## Final Technical Report

### Octanol-Water Partition Coefficients by Capillary Electrophoresis F49620-94-1-0281

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The question of how to assess bioavailability has received much attention. Bioavailability is most often approximated by the distribution of the solute in question between two phases, most often bulk phases, of water and an immiscible organic solvent. Since the inception of reversed phase liquid chromatography there have been many attempts to correlate chromatographic retention with bioavailability and the most often used bulk measure, the octanol-water partition coefficient. An entire field has developed around this research, referred to as Quantitative Structure Activity Relationships (QSAR), or where chromatographic retention is the measured parameter, Quantitative Structure Retention Relationships (QSRR). Yet with present technology, these attempts are inevitably doomed to failure. On the one hand, bulk phases are not appropriate for modeling a partitioning process in an interphase such as biological membranes, and while chromatographic stationary phases can be argued as having similar structure to a membrane because of chain organization, the density of the grafted chains is much too low to provide a suitable model. It is these problems which we have come to understand and propose to address.

Recent statistical mechanical theory developed by Dill has shown that the partitioning of solutes between a bulk phase and an interphase, such as a bilayer membrane, is controlled by the entropy of mixing, the configurations of the chains, and the contact interactions between solute and chains and solute and bulk solvent. We have previously developed new synthetic methodology which yields reversed phase stationary phases of significantly higher bonding density than commercially available phases, and we have shown partitioning of solutes into these phases follows the theory developed by Dill. In our "parent" grant (Thermodynamically Correct Bioavailability Estimations, AFOSR 91-0254), we are investigating the utility of these high density phases for the modeling of bioavailability of various solutes. Instead of the traditional correlations between chromatographic retention and octanol-water partition coefficients, we are investigating correlations between chromatographic retention and physiologically relevant events, such as bioaccumulation. We are greatly encouraged with the results shown to date, and feel that these high density phases provide a significantly better estimation of bioavailability and bioaccumulation than other models.

While our parent grant was designed to improve the direct estimation of biological partitioning processes, the great majority of scientists currently use octanol-water partition coefficients. We have investigated the use of capillary electrophoresis (CE) for the modeling of the octanol-water partition coefficient, and the relevant biological partitioning processes the octanol-water partition coefficient is meant to model. There are literally hundreds of papers reporting the use of reversed-phase liquid chromatography (RPLC) for the estimation of octanol-water partition coefficients, with correlation coefficients reported from approximately 0.5 to 0.999, depending on the particular column and compounds tested. RPLC will never be a reliable method for octanol-water estimations, however, because of the great variability in the chemistry of the stationary phase from column to column. Capillary electrophoresis is a much simpler system, as there is no true stationary phase, and there should then be dramatically less variation from laboratory to laboratory.

We have shown that CE can give a *single point* estimate of the octanol-water partition coefficient. Specifically, micellar electrokinetic capillary chromatography (MECC), the micellar variant of the CE experiment, was evaluated as an *a priori* predictor of n-octanol-water partition coefficients ( $\log K_{ow}$ ). Retention measurements for over 100 solutes with widely varying functionality were used to construct a universal calibration for the estimation of octanol-water partition coefficients with  $r^2 = 0.835$ . The calibration covers in excess of 9 orders of magnitude in  $\log K_{ow}$  and 4 orders of magnitude in log capacity factor. If solute size, structure, and hydrogen-bonding character are known, accuracy can be increased by use of improved calibrations. This method reduces the laboratory-to-laboratory variability and the long analysis time due to the multiple mobile phases necessary in current HPLC methods for estimating  $\log K_{ow}$  while retaining many of the desired advantages of chromatographic techniques.

In summary, we have met the goals of our proposal, and these results have been published in the open literature. Following is a list of refereed papers which acknowledge AFOSR support.

1. "Microscopic Order as a Function of Surface Coverage in Alkyl Modified Silicas: Spin Probe Studies", Paul B. Wright, Edward Lamb, John G. Dorsey and Robert G. Kooser, *Anal. Chem.*, **64**, 785-789 (1992).
2. "Temperature Dependence of Retention in Reversed Phase Liquid Chromatography: Stationary Phase Considerations", Lynn A. Cole and John G. Dorsey, *Anal. Chem.*, **64**, 1317-1323 (1992).
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4. "Liquid Chromatography: Theory and Methodology", John G. Dorsey, Joe P. Foley, William T. Cooper, Robert A. Barford and Howard G. Barth, *Anal. Chem.*, **64**, 353R-389R (1992).
5. "Accurate Determination of  $\log k'_W$  in Reversed Phase Liquid Chromatography: Implications for Quantitative Structure Retention Relationships", Mei-Ming Hsieh and John G. Dorsey, *J. Chromatogr.*, **631**, 63-78 (1993).
6. "The Effect of Stationary Phase Solvation on Shape Selectivity in Reversed Phase Liquid Chromatography", Steven R. Cole and John G. Dorsey, *J. Chromatogr.*, **635**, 177-186 (1993).
7. "Phase Transitions of Reversed Phase Stationary Phases: Cause and Effects in the Mechanism of Retention", John F. Wheeler, Thomas L. Beck, S. J. Klatte, Lynn A. Cole and John G. Dorsey, *J. Chromatogr.*, **656**, 317-333 (1993).

8. "Hydrophobicity Estimations by Reversed Phase Liquid Chromatography: Implications for Biological Partitioning Processes", John G. Dorsey and Morteza G. Khaledi, *J. Chromatogr.*, 656, 485-499 (1993).
9. "Retention Mechanisms of Bonded Phase Liquid Chromatography", John G. Dorsey and William T. Cooper, *Anal. Chem.*, 66, 857A-867A (1994).
10. "Liquid Chromatography: Theory and Methodology", John G. Dorsey, William T. Cooper, John F. Wheeler, Howard G. Barth and Joe P. Foley, *Anal. Chem.*, 66, 500R-546R (1994).
11. "Bioavailability Estimation by Reversed-Phase Liquid Chromatography: High Bonding Density C-18 Phases for Modeling Biopartitioning Processes", Mei-Ming Hsieh and John G. Dorsey, *Anal. Chem.*, 67, 48-57 (1995).
12. "n-Octanol-Water Partition Coefficient Estimation by Micellar Electrokinetic Capillary Chromatography", Bradford J. Herbert and John G. Dorsey, *Anal. Chem.*, 67, 744-749 (1995).
13. "Silver (I) Mediated Separations by Capillary Zone Electrophoresis and Micellar Electrokinetic Chromatography: Argentation Electrophoresis", Paul B. Wright and John G. Dorsey, *Anal. Chem.*, 68, 415-424 (1996).
14. "The Informational Orthogonality of 2-Dimensional Chromatographic Separations", Patrick J. Slonecker, Xiaodong Li, Thomas H. Ridgway and John G. Dorsey, *Anal. Chem.*, 68, 682-689 (1996).
15. "Liquid Chromatography: Theory and Methodology", John G. Dorsey, William T. Cooper, Barbara A. Siles, Joe P. Foley and Howard G. Barth, *Anal. Chem.*, 68, 515R-568R (1996).
16. "Mobile Phase Additives for Enhanced Peptide Separations in Reversed Phase Liquid Chromatography", Steven R. Cole and John G. Dorsey, *Biomed. Chromatogr.*, in press.
17. "Characterization of Conventional Chemically-Bonded Liquid Chromatographic Stationary Phases by Raman Spectroscopy: The Effect of Ligand Type", Charles A. Doyle, Thomas J. Vickers, Charles K. Mann and John G. Dorsey, *J. Chromatogr.*, submitted.
18. "Evaluation of an AOT-Decane Water-in-Oil Microemulsion as a Medium for Capillary Electrophoresis", Carol A. Fung Kee Fung and John G. Dorsey, *J. Chromatogr.*, submitted.